

General

Guideline Title

Individualized medication of voriconazole: a practice guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society.

Bibliographic Source(s)

Chen K, Zhang X, Ke X, Du G, Yang K, Zhai S. Individualized medication of voriconazole: a practice guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Beijing (China): Chinese Pharmacological Society; 2017. 28 p. [59 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the level of evidence (A-E) and strength of recommendation (1, 2) are provided at the end of the "Major Recommendations" field.

Domain 1: Therapeutic Drug Monitoring

Question 1: What Are the Indications for Therapeutic Drug Monitoring (TDM) of Voriconazole (VORI)?

Recommendation 1: The TDM of VORI is recommended for patients with hepatic dysfunction, concomitant drugs that potentially influence VORI pharmacokinetics (PK), cytochrome P450 2C19 (CYP450 2C19) mutants, poor response or adverse events, or life-threatening fungal infections (1D-E, strong recommendation, very low quality of evidence to expert opinion).

Recommendation 2: TDM of VORI is suggested for patients with conditions other than those mentioned in recommendation 1 (2B-D, conditional recommendation, moderate to very low quality of evidence).

Question 2: Which Parameter Should Be Monitored for VORI, the Peak or Trough Blood Concentration?

Recommendation 3: The steady-state trough blood concentration of VORI is recommended to be monitored (1B, strong recommendation, moderate quality of evidence).

Question 3: When Should the Initial Blood Sample Be Obtained to Perform TDM of VORI?

Recommendation 4: When the loading dose of VORI is given, an initial blood sample is suggested to be obtained no earlier than immediately before the 5th dose (on the 3rd day of treatment) (2D, conditional recommendation, very low quality of evidence).

Question 4: What Is the Target Trough Blood Concentration of VORI?

Recommendation 5: The trough blood concentration of VORI is recommended to be maintained above $0.5 \text{ mg} \cdot \text{L}^{-1}$ (1B, strong recommendation, moderate quality of evidence).

Recommendation 6: The trough blood concentration of VORI is recommended to be maintained below $5 \text{ mg} \cdot \text{L}^{-1}$ (1B, strong recommendation, moderate quality of evidence).

Question 5: Under What Conditions Should TDM of VORI Be Repeated?

Recommendation 7: TDM of VORI is recommended to be repeated when adjusting the VORI dosing regimen, patients show a poor response or adverse events, or when initiating or withdrawing concomitant drugs that potentially influence VORI PK (1E, strong recommendation, expert opinion).

Question 6: How Should the VORI Dosing Regimen Be Adjusted if Necessary?

Recommendation 8: Population PK methods are suggested to be used to adjust the VORI dosing regimen when a population PK model based on a native population is available (2E, conditional recommendation, expert opinion).

Recommendation 9: If the patient's steady-state trough blood concentration of VORI is below $0.5 \text{ mg} \cdot \text{L}^{-1}$ or the response is poor, maintaining dosage of VORI is suggested to be increased by 50%, followed by dosage adjustment based on the blood concentration (2D, conditional recommendation, very low quality of evidence).

Recommendation 10: If the patient's steady-state trough blood concentration of VORI is within $5\text{--}10 \text{ mg} \cdot \text{L}^{-1}$ without \geq grade 2 adverse events, maintaining dosage of VORI is suggested to be decreased by 20%, followed by dosage adjustment based on the blood concentration (2D, conditional recommendation, very low quality of evidence).

Recommendation 11: If the patient's steady-state trough blood concentration of VORI is above $10 \text{ mg} \cdot \text{L}^{-1}$ or has grade 2 adverse events, VORI administration is suggested to be skipped once, with the maintenance dosage decreased by 50%, followed by dosage adjustment based on the blood concentration (2D, conditional recommendation, very low quality of evidence).

Domain 2: Special Groups of Patients

Question 7: How Should VORI Be Administered to Patients with Severe Hepatic Dysfunction?

Recommendation 12: For patients with severe hepatic dysfunction, VORI is not suggested for first-line treatment. After balancing the benefits and harms, VORI can be used for these patients under rigorous TDM and hepatic function monitoring (2D, conditional recommendation, very low quality of evidence).

Domain 3: Drug Safety

Question 8: What Measures Should Be Taken to Rescue VORI Overdose?

Recommendation 13: Temporarily withdrawing VORI, TDM and supportive treatment with evident adverse events are recommended to rescue VORI overdose (1D, strong recommendation, very low quality of evidence).

Question 9: What Measures Should Be Taken to Address Common Adverse Events of VORI?

Recommendation 14: The recommended indications to withdraw VORI are as follows: alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) level above 5 upper limits; total bilirubin (T-Bil) level above 3 upper limits; severe neurologic, psychiatric or eyesight symptoms with limiting self-care activities of daily living (ADL); skin rash covering $>30\%$ body surface area (BSA), with limiting self-care ADL or sleep or with oral corticosteroid indicated (1E, strong recommendation, expert opinion).

Recommendation 15: The recommended indications to decrease the VORI dosage are as follows: ALT or AST level above 3 upper limits; ALP or GGT level above 2.5 upper limits; T-Bil level above 1.5 upper limits; moderate neurologic, psychiatric or eyesight symptoms with limiting instrumental use ADL; skin rash covering between 10% and 30% BSA, with limiting instrumental use ADL or with oral medications indicated (2E, conditional recommendation, expert opinion).

Question 10: What Is the Compatibility of VORI?

Recommendation 16: Intravenous VORI is recommended to be administered alone and is incompatible with any other drugs (1E, strong

recommendation, in vitro evidence).

Recommendation 17: VORI is NOT recommended to share the same Y-site tube with the drugs below: conventional amphotericin B, cefepime, cyclosporine, dantrolene, busulfan, diazepam, liposomal daunorubicin, idarubicin, mitoxantrone, moxifloxacin, nitroprusside, pantoprazole, phenytoin, thiopental, and tigecycline. Flushing the infusion line is required if VORI is used consecutively with these drugs (1E, strong recommendation, in vitro evidence).

Domain 4: Off-indication Use

Question 11: What Sites of Fungal Infections Can Be Treated by VORI Other Than Those of Respiratory, Central Nervous System and Blood Stream Infections?

Recommendation 18: On the condition of pathogens sensitive to VORI, VORI is suggested to treat the following infections: fungal keratitis, fungal endophthalmitis, bone and joint fungal infections, fungal peritonitis and fungal endocarditis (2D, conditional recommendation, very low quality of evidence).

Domain 5: Drug-Drug Interaction

Question 12: What Measures Should Be Taken to Manage the Concomitant Use of VORI and Drugs That Potentially Influence VORI PK?

Question 13: What Initial Dosage of VORI Should Be Taken When Using Drugs That Potentially Influence VORI PK Concomitantly?

Recommendation 19: Due to their significant impacts on VORI, the following drugs are not recommended to be used concomitantly with VORI: efavirenz (400 mg daily [QD]), ritonavir (400 mg every 12 hours [Q12H]), St. John's wort, rifampin, and phenobarbital (1A-D, strong recommendation, high to very low quality of evidence).

Recommendation 20: Due to their significant impacts on VORI, the following drugs are not suggested to be used concomitantly with VORI: secobarbital and amobarbital (2E, conditional recommendation, expert opinion).

Recommendation 21: The VORI dosage is recommended to be increased to 400 mg Q12H when used concomitantly with the following drugs: efavirenz (300 mg QD) and phenytoin (1D, strong recommendation, very low quality of evidence).

Recommendation 22: The VORI dosage is suggested to be increased when used concomitantly with the following drugs: rifabutin, carbamazepine, and nevirapine. For rifabutin, the VORI dosage is suggested to be increased to 350 mg Q12H (2D-E, conditional recommendation, very low quality of evidence to expert opinion).

Recommendation 23: The efficacy and safety of VORI are recommended to be closely monitored when used concomitantly with the following drugs: glucocorticoids and cimetidine (1D, strong recommendation, very low quality of evidence).

Recommendation 24: The efficacy and safety of VORI are suggested to be closely monitored when used concomitantly with the following drugs: mycophenolate mofetil, ritonavir (100 mg Q12H), indinavir, atazanavir, saquinavir, rilpivirine, etravirine, *Ginkgo biloba*, omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, erythromycin, azithromycin, clarithromycin, and norethindrone/ethinyl estradiol (2B-E, conditional recommendation, moderate quality of evidence to expert opinion).

Question 14: Which Drugs Are Potentially Influenced by VORI?

Recommendation 25: VORI has a significant impact on the following drugs, whose efficacy and safety are recommended to be closely monitored and whose use concomitantly with VORI should be avoided in certain circumstances: oxycodone, methadone, fentanyl, alfentanil, diclofenac, etoricoxib, meloxicam, midazolam, etravirine, efavirenz, cyclosporine, tacrolimus, sirolimus, everolimus, norethindrone, ethinyl estradiol, glimepiride, nifedipine, simvastatin, vincristine, and warfarin (1A-D, strong recommendation, high to very low quality of evidence).

Recommendation 26: VORI has a significant impact on the following drugs, whose efficacy and safety are suggested to be closely monitored and whose use concomitantly with VORI should be avoided in certain circumstances: tilidine, buprenorphine, ibuprofen, venlafaxine, zolpidem, diazepam, estazolam, lorazepam, alprazolam, triazolam, ritonavir, indinavir, atazanavir, saquinavir, rilpivirine, nevirapine, tolbutamide, glipizide, glyclazide, glibenclamide, glimepiride, lovastatin, atorvastatin, digoxin, ergot alkaloid, cisapride, quinidine, terfenadine, and acenocoumarol (2B-E, conditional recommendation, moderate quality of evidence to expert opinion).

Refer to the original guideline document for information on Domain 6: Questions That Failed to Formulate Recommendations.

Definitions

	Strong recommendation (1)	Conditional recommendation (2)
High (A)	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.	The best action may differ depending on circumstances or patients or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Moderate (B)	Recommendation can apply to most patients in most circumstances. Further research is likely to have an important impact on confidence in the effect.	Alternative approaches are likely to be better for some patients under some circumstances. Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low (C)	Recommendation may change when higher-quality evidence becomes available. Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate.	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low (D)	Recommendation may change when higher-quality evidence becomes available. Any estimate of effect is very uncertain.	Other alternatives may be equally reasonable. Any estimate of effect is very uncertain.
Expert opinion or in vitro evidence (E)	No human study is available. Recommendations can apply to most patients in most circumstances theoretically. Recommendation may change when higher-quality evidence becomes available.	No human study is available. Other alternatives may be equally reasonable. Any estimate of effect is very uncertain.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Invasive fungal diseases

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Critical Care

Hematology

Infectious Diseases

Internal Medicine

Medical Genetics

Oncology

Pediatrics

Pharmacology

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Health Care Providers

Hospitals

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To develop an evidence-based practice guideline for individualized medication of voriconazole (VORI) to improve the efficacy, safety and economy of VORI use in China
- To provide guidance on 5 domains of individualized medication of VORI: therapeutic drug monitoring (TDM), special groups of patients, drug safety, off-indication use, and drug-drug interactions

Target Population

Adults and children with invasive fungal diseases taking voriconazole

Interventions and Practices Considered

1. Indications for therapeutic drug monitoring (TDM) of voriconazole (VORI)
2. Monitoring trough blood concentrations of VORI
3. Obtaining initial blood concentrations of VORI
4. Maintaining target blood concentrations of VORI
5. Adjusting the VORI dosing regimen using a population pharmacokinetic model based on response and toxicity
6. Considerations for patients with hepatic dysfunction
7. Measures to maintain drug safety (dosage reduction or drug withdrawal)
8. Measures to avoid unsafe drug interactions
9. Considerations for off-label use

Major Outcomes Considered

- Treatment response
- Prophylaxis failure
- Infection-related mortality
- Hepatotoxicity (separately from other adverse effects)
- Other adverse effects of voriconazole (nephrotoxicity, nervous system/psychiatric disorders, visual disturbance, skin disorders)

- Economic outcomes
- Length of hospital stay

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Guideline Consensus Panel (GCP) identified 18 questions. The Guideline Development Group (GDG) systematically collected related evidence and completed 9 systematic reviews (3 were further updated). References were searched on PubMed, EMBASE, Cochrane Library, clinicaltrials.gov, and 3 Chinese databases (CNKI, Wanfang, and Sinomed) until January 26, 2016 using the single search term "voriconazole". For some of the questions that could not be answered by a systematic review, evidence was also collected systematically via a process of searching and identifying references. Only data from Asian people were considered for safety outcomes unless the data were only available from non-Asian people. Pharmacokinetic outcomes were used as surrogates of efficacy and safety outcomes. In addition, the GDG investigated 119 patients from 9 Chinese hospitals who were taking VORI on their values and preferences towards therapeutic drug monitoring (TDM) of VORI and cytochrome P2C19 (CYP2C19) gene test. The hospitals were selected with regards to regions distribution, and the patients were selected through convenience sampling. A 6-minute video was played for investigated patients regarding background information for the questionnaire (i.e., explanation of medical vocabulary, potential benefits and harms of voriconazole therapeutic drug monitoring [VORI TDM] and CYP2C19 gene test, costs). All the research results were presented to the GCP while formulating recommendations.

Refer to the full systematic reviews and meta-analyses for specific search information and results (see the "Availability of Companion Documents" field).

Number of Source Documents

Refer to the individual systematic reviews and meta-analyses (see the "Availability of Companion Documents" field) for a breakdown of the number of studies included and excluded and reasons for exclusion.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence and Strength of Recommendation Using the GRADE Approach

	Strong recommendation (1)	Conditional recommendation (2)
High (A)	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.	The best action may differ depending on circumstances or patients or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Moderate (B)	Recommendation can apply to most patients in most circumstances. Further research is likely to have an important impact on confidence in the effect.	Alternative approaches are likely to be better for some patients under some circumstances. Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low (C)	Strong recommendation (1) Recommendation may change when higher-quality evidence becomes available. Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate.	Conditional recommendation (2) Other alternatives may be equally reasonable. Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low (D)	Recommendation may change when higher-quality evidence becomes available. Any estimate of effect is very uncertain.	Other alternatives may be equally reasonable. Any estimate of effect is very uncertain.
Expert opinion or in vitro evidence (E)	No human study is available. Recommendations can apply to most patients in most circumstances theoretically. Recommendation may change when higher-quality evidence becomes available.	No human study is available. Other alternatives may be equally reasonable. Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Refer to the full systematic reviews and meta-analyses for specific information on the methods used in each review (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Through a 3-round Delphi and Grading of Recommendations Assessment, Development and Evaluation (GRADE) grid methodology, the Guideline Consensus Panel (GCP) voted on draft recommendations regarding the benefits and harms profile, quality of evidence, patients' views and preferences, and costs. GRADE evidence tables, evidence summary tables, results of patients' preferences investigation, and costs analyses were presented to the GCP. A strong recommendation required a $\geq 70\%$ approval and a conditional recommendation $\geq 50\%$. The percentage for opposing a consensus recommendation was $\leq 20\%$.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

- A strong recommendation (number '1' used) is one that can apply to most patients in most circumstances.
- A conditional recommendation (number '2' used) is one for which the desirable effects of adherence probably outweigh the undesirable effects, but the Guideline Steering Committee and the Guideline Consensus Panel are not sufficiently confident about these trade-offs.

Cost Analysis

A formal cost analysis was not performed. Published cost analyses were reviewed, and a reference related to cytochrome P450 (CYP450) 2C19 gene test was identified.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

After approval of the draft recommendations by the Guideline Steering Committee (GSC), they were published on the official Web site of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society, and were further submitted to 20 front-line physicians and pharmacists, as well as 1 patient, for external review. Their feedback was discussed by the GSC, and revisions of the draft recommendations were made. The final version of 26 recommendations was formulated and approved by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Voriconazole blood trough concentrations have been shown to be associated with efficacy and toxicity, and thus therapeutic drug monitoring (TDM) is currently the best option to guide dose optimization and improve clinical outcomes. Recently, voriconazole dosed according to the prescribing information, and then followed by TDM of trough concentrations to adjust the dose, was found to be beneficial. Notably, a therapeutic failure with voriconazole is potentially life threatening.

Potential Harms

- Common adverse events of voriconazole include hepatotoxicity, nervous system/psychiatric disorders, visual disturbance, and skin disorders.
- High trough blood concentration of voriconazole is found to be related to a higher incidence of hepatotoxicity.
- Special precautions need to be taken when voriconazole is co-administered with known cytochrome P450 (CYP450) inducers, inhibitors, or substrates.

Refer to the systematic reviews "The influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole," "Effect of cytochrome P-450 inhibitors on pharmacokinetics and safety of voriconazole," "Influence of voriconazole on pharmacokinetics and safety of combined drugs" (see the "Availability of Companion Documents" field) for additional information on drug interactions.

Contraindications

Contraindications

The combination use of high-dose efavirenz, high-dose ritonavir, St John's wort, rifampin, or phenobarbital with voriconazole is contraindicated.

Refer to the systematic review "The influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole" (see the "Availability of Companion Documents" field) for additional information on drug interactions.

Intravenous voriconazole is incompatible with any other drugs and is NOT recommended to share the same Y-site tube with the following drugs:

conventional amphotericin B, cefepime, cyclosporine, dantrolene, busulfan, diazepam, liposomal daunorubicin, idarubicin, mitoxatrone, moxifloxacin, nitroprusside, pantoprazole, phenytoin, thiopental, and tigecycline.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Chen K, Zhang X, Ke X, Du G, Yang K, Zhai S. Individualized medication of voriconazole: a practice guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Beijing (China): Chinese Pharmacological Society; 2017. 28 p. [59 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017

Guideline Developer(s)

Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society - Medical Specialty Society

Source(s) of Funding

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Guideline Steering Committee and the Guideline Consensus Panel were partly funded by Pfizer Investment Ltd. The guideline developers guarantee that Pfizer Investment Ltd. was not involved in guideline development, and guideline development was not influenced by Pfizer Investment Ltd. Members of the Guideline Steering Committee, the Guideline Consensus Panel and the Guideline Development Group did not have contact with Pfizer Investment Ltd.

Guideline Committee

Guideline Steering Committee

Guideline Consensus Panel

Guideline Development Group

Composition of Group That Authored the Guideline

Guideline Steering Committee: Guanhua Du, Institute of Materia Medica, Chinese Academy of Medical Sciences; Xiaoyan Ke, Peking University Third Hospital; Kehu Yang, Evidence-based Medicine Center, Lanzhou University; Suodi Zhai, Peking University Third Hospital; Xianglin Zhang, China-Japan Friendship Hospital

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Financial Disclosures/Conflicts of Interest

Every member of the Guideline Steering Committee, the Guideline Consensus Panel and the Guideline Development Group were required to complete a declaration of conflicting interests form before participating in guideline development and none had any to disclose.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society Web site](#) .

Availability of Companion Documents

The following systematic reviews are available:

- Li TY, Liu W, Chen K, Liang SY, Liu F. The influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole: a systematic review. *J Clin Pharm Ther.* 2017 Apr;42(2):135-46. Available from the [Journal of Clinical Pharmacy and Therapeutics Web site](#) .
- Li X, Yu C, Wang T, Chen K, Zhai S, Tang H. Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis. *Eur J Clin Pharmacol.* 2016 Oct;72(10):1185-93. Available from the [European Journal of Clinical Pharmacology Web site](#) .
- Jin H, Wang T, Falcione BA, Olsen KM, Chen K, Tang H, Hui J, Zhai S. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2016 Jul;71(7):1772-85. Available from the [Journal of Antimicrobial Chemotherapy Web site](#) .
- Liu Y, Liang S, Chen K, Zhang F, Liu F. Influence of voriconazole on pharmacokinetics and safety of combined drugs: a systematic review. *J Chinese Pharm Sci.* 2016 Nov. 25(11):785-98. Available from the [Journal of Chinese Pharmaceutical Sciences Web site](#) .
- Yang H, Chen K, Liang S, Zhai S, Yi Z. Effect of cytochrome P-450 inhibitors on pharmacokinetics and safety of voriconazole. *J Chinese Pharm Sci.* 2017 Mar;26(3):202-11. Available from the [Journal of Chinese Pharmaceutical Sciences Web site](#) .

Other Chinese documents with English abstracts (Protocol, questions and outcomes, systematic review, patients' preference, recommendations consensus, external review) are available from the [Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 10, 2017. The information was verified by the guideline developer on June 5, 2017.

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